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Our Case No. 7814/42

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Milan Mrksich et al.

Serial No. 09/689,263

Filing Date: October 11, 2000

For SURFACE MODIFYING COMPOSITION

Examiner David M. Naff

Group Art Unit No. 1651

APPELLANTS' BRIEF

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is an appeal from the Final Rejection dated July 29, 2003, of Claims 19-36, 41, 43, 44 and 49-58, which are all the claims pending in the above-captioned case.

(1) REAL PARTY IN INTEREST

The present application is owned by The University of Chicago.

(2) RELATED APPEALS AND INTERFERENCES

There are no known appeals or interferences that will directly affect or be directly affected by or have a bearing on this appeal.

(3) STATUS OF CLAIMS

Claims 19-36, 41, 43, 44 and 49-58, as set forth in appellants' Amendment and Request for Reconsideration filed May 13, 2003, stand rejected and remain pending. All claims are hereby appealed.

(4) STATUS OF AMENDMENTS

A Request for Reconsideration was filed November 25, 2003, after Final Rejection. The Advisory Action of December 24, 2003, indicates that this Request for Reconsideration was considered. A Supplemental Response to Final Office Action was filed on January 14, 2004. No amendments were made in either of these filings, and thus the claims are in the form as referred to in the Final Rejection of July 29, 2003; and as set forth in appellants' aforementioned Amendment of May 13, 2003.

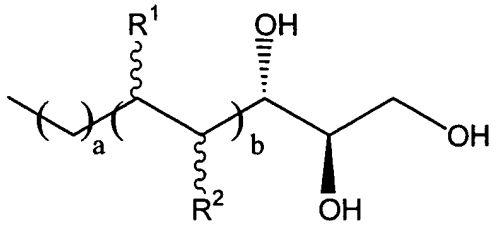
(5) SUMMARY OF INVENTION

The present invention relates to materials and methods for forming stable patterns of cultured cells, which are useful in fields such as diagnostics and drug development. In particular, the present invention relates to self-assembled monolayers (SAMs) of alkanethiolates on a substrate, where the alkanethiolates provide for a surface that is inert to the adsorption of proteins and cells.

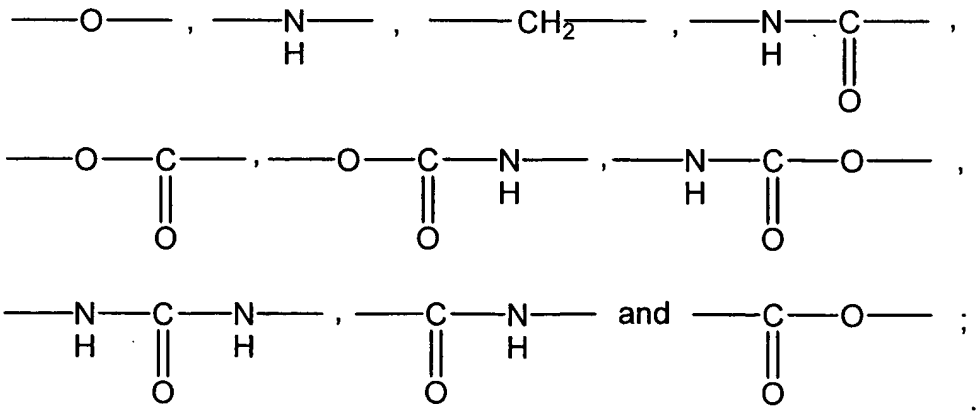
In one embodiment of the invention, the substrate has a gold surface layer with a plurality of alkanethiolate groups of the following formula, or its enantiomers, on at least a portion of the suface layer:

Surf——S——L——Q——T

In this formula, "Surf–" designates where the alkanethiolate attaches to the surface layer (p.10, lines 9-19). The "–T" group in this structure is a terminal group having the following formula:



Within the formula for the "–T" group, R^1 and R^2 are each individually selected from the group consisting of H and OH; a is 0 to 3; b is 0 to 3; ∿∿∿ indicates that the chirality of the carbon atom to which it is attached is either R or S (p.7, line 30 – p.8, line 5). The "–L–" group is represented as $-(A_x-B_y-E_z-D)_w-$; where each A, B, E and D are individually $-C(R_AR_A')-$, $-C(R_BR_B')-$, $-C(R_ER_E')-$, and $-C(R_DR_D')-$, respectively; each R_A, R_B, R_E and R_D are individually H, or any two of R_A, R_B, R_E and R_D together form a bond, or R_A, R_B, R_E and R_D together with the atoms to which they are bonded form a six-membered aromatic ring; each R_A', R_B', R_E' and R_D' are individually H, or any two of R_A', R_B', R_E' and R_D' together form a bond, or R_A', R_B', R_E' and R_D' together with the atoms to which they are bonded form a six-membered aromatic ring; and each x, y and z are individually either 0 or 1; w is 1 to 5 (p.7, lines 13-20). The "–Q–" group (p.7, lines 21-end) is selected from the group consisting of:



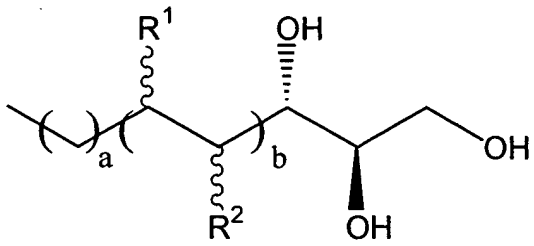
In a second embodiment of the invention, the substrate has a gold surface layer with a monolayer containing alkanethiolate groups on at least a portion of the surface layer (p.10, lines 9-13). The monolayer of this embodiment does not fail a cell patterning test at 12 days, which test is described in the specification at page 12, lines 1-16.

In a third embodiment of the invention, a cell chip contains a substrate as described above and contains cells on the substrate (p.11, lines 15-21).

In a fourth embodiment of the invention, a method of making a substrate includes contacting a gold-containing surface with an alkanethiol of the following formula or its enantiomers:

HS——L——Q——T

(p.10, lines 9-19). In this formula, the "–T" group is a terminal group having the following formula:



Within the formula for the "–T" group, R^1 and R^2 are each individually selected from the group consisting of H and OH; a is 0 to 3; b is 0 to 3; ∿∿∿ indicates that the chirality of the carbon atom to which it is attached is either R or S (p.7, line 30 – p.8, line 5; p.10, line 18). The "–L–" and "–Q–" groups are as set forth above (p.7, lines 13-end; p.10, line 18).

In a fifth embodiment of the invention, a method of making a cell chip includes contacting cells with a substrate as described above (p.11, lines 15-21).

(6) ISSUE

1. Whether Claims 19, 29, 30, 36 and 41 are anticipated under 35 USC § 102 by or, in the alternative, are obvious under 35 USC § 103 over Chapman et al. (*J. Am. Chem. Soc.* 2000, *122* (34), 8303-8304).

2. Whether Claims 29, 36, 57 and 58 are obvious under 35 USC § 103 over Mrksich et al. (A18; *Am. Chem. Soc. Symp. Ser.* 1997, *680*, 361-373), in view of Hodneland et al. (I) (A7; *J. Am. Chem. Soc.* 2000, *122* (17), 4235-4236), Houseman et al. (A9; *Angew. Chem. Int. Ed.* 1999, *38* (6), 782-785) and Sigal et al. (A25; *J. Am. Chem. Soc.* 1998, *120* (14), 3464-3473), and further in view of Deng et al. (A3; *J. Am. Chem. Soc.* 1996, *118* (21), 5136-5137) and Hodneland et al. (II) (A8; *Langmuir* 1997, *13* (23), 6001-6003).

3. Whether Claims 29, 36, 57 and 58 are obvious under 35 USC § 103 over Mrksich et al., Hodneland et al. (I), Houseman et al. or Sigal et al., in view of Chapman et al.

4. Whether Claims 19-36, 41, 43, 44 and 49-58 are obvious under the judicially created doctrine of obviousness-type double patenting over claims 1-117 of U.S. Patent Application Serial No. 09/923,760 or claims 1-41 of U.S. Patent Application Serial No. 09/797,166 (now U.S. Patent No. 6,764,768 B2), in view of Chapman et al.

(7) GROUPING OF CLAIMS

For the purposes of this appeal, the claims stand or fall together.

(8) ARGUMENT

1. Claims 19, 29, 30, 36 and 41 are not anticipated by, nor obvious over, Chapman et al.

Claims 19, 29, 30, 36 and 41 stand rejected under 35 U.S.C. § 102(a) or 103(a) as allegedly anticipated or obvious over Chapman et al. (*J. Am. Chem. Soc.* **2000**, *122* (34), 8303-8304). The Examiner asserts that structure no. 2 in Figure 1 of Chapman et al. discloses a group for an alkanethiol moiety that is the same as the "–T" group recited in the claims. The Examiner contends, without recital of a source of information, that an enantiomer of the disclosed group would be an obvious choice expected to have the same function as the disclosed group. Appellants respectfully traverse the Examiner's position regarding Chapman et al.

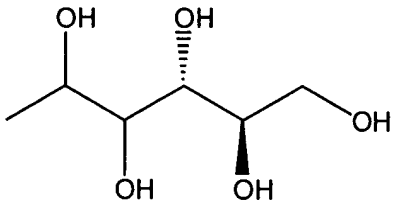
First and foremost, the Chapman et al. reference is not a proper reference under 35 U.S.C. § 102(a). In the Request for Reconsideration filed November 25, 2003, appellants submitted Declarations Pursuant to 37 CFR 1.131 from inventors Milan Mrksich and Yan-Yeung Luk. These Declarations assert that the inventors had completed, in the United States, the invention described and claimed in the present application prior to August 12, 2000, the earliest publication date of Chapman et al. The evidence supporting the inventors' assertion includes the publication Luk, Y-Y.; Kato, M. and Mrksich, M. "Self-Assembled Monolayers of Alkanethiolates Presenting Mannitol Groups Are Inert to Protein Adsorption and Cell Attachment" *Langmuir* **2000**, *16*, 9604-9608, hereinafter Luk et al. The Advisory Action of December 24, 2003 contends that the evidence in the Declarations is insufficient to establish a date of invention prior to the publication date of Chapman et al., because the Luk et al. reference establishes information to "overcome Chapman et al. only with respect to the species shown by Figure 1" (Advisory Action, p. 2).

Applicants respectfully note that the evidence presented in the Declarations includes the entire disclosure of the Luk et al. article, as stated at section 3(a) of each of the inventors' Declarations filed November 25, 2003. The Declarations clearly do not limit the evidence to the single species shown in Figure 1(B) on p. 9605 of the Luk et al.

reference. The specific recital of this species at section 3(b) of the Declarations simply provides an example of the genus of alkanethiols as set forth at independent claims 19 and 41.

Contrary to the Examiner's contention, Luk et al. is a good and appropriate proof of appellants' having the claimed invention in hand prior to the publication date of Chapman et al. For example, the Examiner previously cited Luk et al. in support of a 35 U.S.C. § 102(a) rejection of all the currently pending claims. In particular, on page 3, lines 21-27 of the Office Action of January 13, 2003, the Examiner states that the Luk et al. article discloses or teaches both a "–T" group and an entire substrate as recited in the claims. Indeed, turning to the Luk et al. article directly, footnote (9) on p. 9605, col. 1 discloses the formation of SAMs of alkanethiols as claimed on gold surfaces (i.e claims 19 and 41). The Luk et al. article also discloses possible variations in the length of the alkanethiols at p. 9605, col. 1 (i.e claims 19 and 41). With respect to cell chips, the Luk et al. article at p. 9605, col. 2 – p. 9606, col. 2 discloses the combination of cells with substrates as recited in the claims (i.e. claims 29, 30 and 36). In addition, the Luk et al. article at p. 9605, col. 2 – p. 9606, col. 1 discloses the measurement of the spreading of cells on surfaces containing the SAMs (i.e. claims 29 and 36). Thus, the Luk et al. article clearly provides evidence of species beyond the one particular structure set forth in the Advisory Action.

Even if, arguendo, the disclosure of Luk et al. was limited to the structure of Figure 1(B) on p. 9605, this structure shows precisely what the Examiner has asserted is shown by Chapman et al., specifically a "–T" group having the structure:



The Examiner has not asserted that the disclosure or teaching of Chapman et al., directed as it is to a study to prepare and screen "surfaces for their ability to resist the adsorption of protein from solution" (Chapman et al., p.8303, col.1), is more broad than the disclosure or teaching of the Luk et al. article. Luk et al. is directed to surfaces that not only prevent adsorption of proteins, but that also can "maintain the patterned

adhesion of cells" (Luk et al., p. 9606, col.2). Differences between a surface that is inert to proteins only and a surface that is inert to both proteins and cells are discussed at p.9606, col.2, first full paragraph.

The inclusion of enantiomers of the alkanethiol or alkanethiolate moieties is a limitation of appellants' independent claims 19 and 41. The Examiner contends that the recital of one chiral form of a useful group, which is included in the Chapman et al. reference, renders obvious its other chiral form, which is not included in that reference. This presumption has no basis or suggestion in the cited references, and appears to be presented in the Final Rejection (p. 2, lines 21-24; p. 3, lines 17-19; and p. 6, lines 6-8) and in the Office Action of January 13, 2003 (p. 3, lines 24-28; p. 4, lines 11-13; and p. 6, lines 12-15) as a recital of the Examiner's personal knowledge. However, this aspect of the claims was first disclosed in appellants' specification. In contrast to the Examiner's contention, it is commonly known that a showing of operativeness in one enantiomeric group is not dispositive of operativeness in that group's opposing enantiomeric form, especially with respect to interactions of the group with proteins and biological substances. See McMurray, J. *Organic Chemistry, 3rd Ed.* Brooks/Cole: Pacific Grove, CA, 1992, pp. 322-324. If the Chapman et al. reference is found appropriate to support an obviousness rejection, then appellants request hereby that the information and reasoning behind the Examiner's statement be reduced to writing in an affidavit, pursuant to 37 CFR § 1.104(d)(2).

In view of the above, Chapman et al. is not a proper reference under 35 U.S.C. § 102(a) or 103(a) because the inventors had completed the invention described and claimed in the present application prior to the earliest publication date of the reference. Accordingly, Chapman et al. cannot anticipate or render obvious claims 19, 29, 30, 36 and 41.

2. Claims 29, 36, 57 and 58 are not obvious over Mrksich et al., in view of Hodneland et al. (I), Houseman et al. and Sigal et al., and further in view of Deng et al. and Hodneland et al. (II).

Claims 29, 36, 57 and 58 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Mrksich et al. (A18; *Am. Chem. Soc. Symp. Ser.* **1997**, *680*, 361-373), in view of Hodneland et al. (I) (A7; *J. Am. Chem. Soc.* **2000**, *122* (17), 4235-4236), Houseman et al. (A9; *Angew. Chem. Int. Ed.* **1999**, *38* (6), 782-785) and Sigal et al. (A25; *J. Am. Chem. Soc.* **1998**, *120* (14), 3464-3473), and further in view of Deng et al. (A3; *J. Am. Chem. Soc.* **1996**, *118* (21), 5136-5137) and Hodneland et al. (II) (A8; *Langmuir* **1997**, *13* (23), 6001-6003). The Examiner asserts that it would be obvious to select preferred alkanethiol or alkanethiolate groups as disclosed in Hodneland (I), Houseman et al., Sigal et al., Deng et al. or Hodneland (II) et al., and that these selected groups could be substituted for the alkanethiol or alkanthiolate moieties in Mrksich et al. The Examiner further asserts that monolayers formed from these selected groups would inherently provide a monolayer that does not fail a cell patterning test at 12 days, wherein the "cell patterning test" of appellants' claimed invention can be any cell patterning test known in the art.

The rejection of the claims under 35 U.S.C. § 103(a) over Mrksich et al., Hodneland et al. (I), Houseman et al., Sigal et al., Deng et al., and Hodneland et al. (II) is respectfully traversed. The cited references, alone or in combination, do not teach or suggest each and every element of the claims. Specifically, the references do not teach or suggest a monolayer that does not fail the cell patterning test defined in appellants' application at 12 days. This characteristic of a monolayer, at least, renders the claimed subject matter unobvious over the cited references taken as a whole. A monolayer that does not fail the cell patterning test at 12 days is more inert to cell adhesion than is a monolayer that fails the cell patterning test at 12 or fewer days. Thus, monolayers of the present invention can extend the time course over which cells can be patterned in culture and can extend the times over which cultured cells can be maintained in patterns.

The term "a cell patterning test" is not any such test known in the art. It is clearly defined in the specification at page 12, lines 1-16. It is not a "preferred" cell patterning test; it is the cell patterning test. It is effectively an instruction to the public for testing whether an arguably infringing substrate is inside or outside the scope of appellants' claimed invention. This definition includes requirements for the preparation of the substrate to be tested (lines 3-5), the type of cells used in the test (lines 5-6), the processing of the cells in preparation for the test (lines 6-8), the application of the cells to the substrate (lines 8-10) the environmental conditions for the test (lines 10-12), and the monitoring of the results of the test (lines 11-14). This definition of "a cell patterning test" is further exemplified in the Examples section of the specification, at least from page 18, line 1 through page 19, line 21.

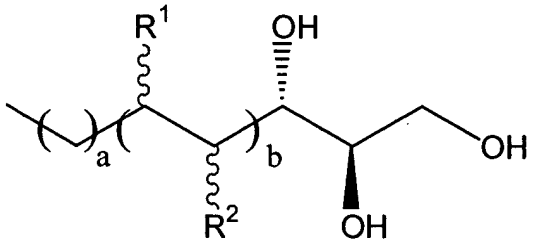
In the Advisory Action, the Examiner maintains that independent claim 29 is not limited to a particular cell patterning test, and that limiting the claims to the definition of "a cell patterning test" in the specification would be equivalent to reading limitations into the claims. However, here, appellants have fully intended to exercise their privilege to be their own lexicographer and to define "a cell patterning test" with the definition found in the specification. Appellants further note that the claims are appropriately examined within the "broadest reasonable interpretation consistent with the specification" (*In re Hyatt*, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000); emphasis added). Here, the breadth of the element in question is limited to what is disclosed, purposely so. Appellants respectfully assert that the meaning of the cell patterning test phrase should not be construed in a "lexicographic vacuum, but in the context of the specification and drawings." *Toro Co. v. White Consolidated Industries Inc.*, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999).

Appellants submit that the definition found in the specification at page 12, lines 1-16, of "a cell patterning test" is the intended meaning of that phrase in independent claim 29. The simple recitation of this defined term is in full compliance with the requirements for claim language and with the stated policies of the U.S. Patent & Trademark Office (MPEP § 2111). However, if it would facilitate a finding of allowability of the claims, appellants would be agreeable to amend claim 29 to include the definition of the cell patterning test, as set forth in the specification.

Because the claims that include the "cell patterning test" element, such as independent claim 29, must be interpreted with respect to the test described at page 12, lines 1-16, and not just any cell patterning test, the cited references, alone or in any combination, do not teach or suggest alkanethiol or alkanethiolate groups that can be selected to provide a monolayer that "does not fail a cell patterning test at 12 days." Accordingly, claims 29, 36, 57 and 58 are not obvious over the cited references, alone or in combination.

3. Claims 19-36, 41, 43, 44 and 49-58 are not obvious over Mrksich et al., Hodneland et al. (I), Houseman et al. or Sigal et al., in view of Chapman et al.

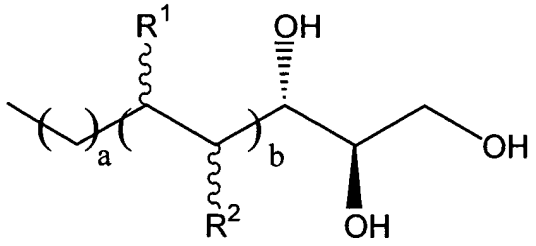
Claims 19-36, 41, 43, 44 and 49-58 were rejected under 35 U.S.C. § 103(a) over Mrksich et al., Hodneland et al. (I), Houseman et al. or Sigal et al., in view of Chapman et al. This rejection of the claims under 35 U.S.C. § 103(a) is respectfully traversed. As fully described at subsection 1 above, Chapman et al. has been sworn behind by the inventors, and is therefore not applicable against the present invention. The remaining references, Mrksich et al., Hodneland et al. (I), Houseman et al. and Sigal et al., alone or in combination, do not teach or suggest each and every element of claims 29, 36, 57 and 58, as noted in subsection 2 above. Specifically, the references fail to teach or suggest at least a "-T" group having the structure:



This "-T" group, at least, renders the claimed subject matter unobvious over the cited references taken as a whole. Accordingly, the remaining references, alone or in combination, are insufficient to provide a *prima facie* case of obviousness against pending claims 19-36, 41, 43, 44 and 49-58.

4. Claims 19-36, 41, 43, 44 and 49-58 are not obvious, under the judicially created doctrine of obviousness-type double patenting, over claims 1-117 of U.S. Patent Application Serial No. 09/923,760 or claims 1-41 of U.S. Patent Application Serial No. 09/797,166 (now U.S. Patent No. 6,764,768 B2), in view of Chapman et al.

Claims 19-36, 41, 43, 44 and 49-58 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-117 of U.S. Patent Application Serial No. 09/923,760 or claims 1-41 of U.S. Patent Application Serial No. 09/797,166 (now U.S. Patent No. 6,764,768 B2), in view of Chapman et al. The rejection of the claims under the judicially created doctrine of obviousness-type double patenting is respectfully traversed. The inapplicability of Chapman et al. as a reference against the pending claims has been addressed above at subsection 1. There is no assertion that the claims of the cited patent applications, alone or in any combination, support any rejection whatsoever in the absence of Chapman et al. Specifically, the cited patent applications fail to teach or suggest at least a "-T" group having the structure:



This "-T" group, at least, renders the claimed subject matter unobvious over the cited applications taken as a whole. Accordingly, no *prima facie* case of obviousness-type double patenting against pending claims 19-36, 41, 43, 44 and 49-58 exists.

5. Conclusion

The cited references, either alone or in combination, do not provide a valid basis for rejection of the present claims. In particular, applying the Chapman et al. reference is inappropriate in view of the inventors' Declarations Pursuant to 37 CFR 1.131, in which they establish a date of invention that predates Chapman et al. The remaining cited references do not teach or suggest alkanethiols or alkanethiolates that can be selected to provide a monolayer having the claimed performance in a cell patterning test. Accordingly, appellants submit that claims 19-36, 41, 43, 44 and 49-58 are fully patentable over the remaining cited references, and the Examiner's rejection should be REVERSED.

Respectfully submitted,

August 27, 2004

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APPENDIX

19. A substrate, comprising:

(i) a surface layer comprising gold, and

(ii) a plurality of moieties, on at least a portion of said surface layer,

wherein said moieties are alkanethiolate moieties of formula (5) or enantiomers of the alkanethiolate moieties of formula (5):

Surf——S——L——Q——T (5);

-L- is $-(A_x-B_y-E_z-D)_w-$;

each A, B, E and D are individually $C(R_AR_A')$-, $-C(R_BR_B')$-, $-C(R_ER_E')$-, and $-C(R_DR_D')$-, respectively;

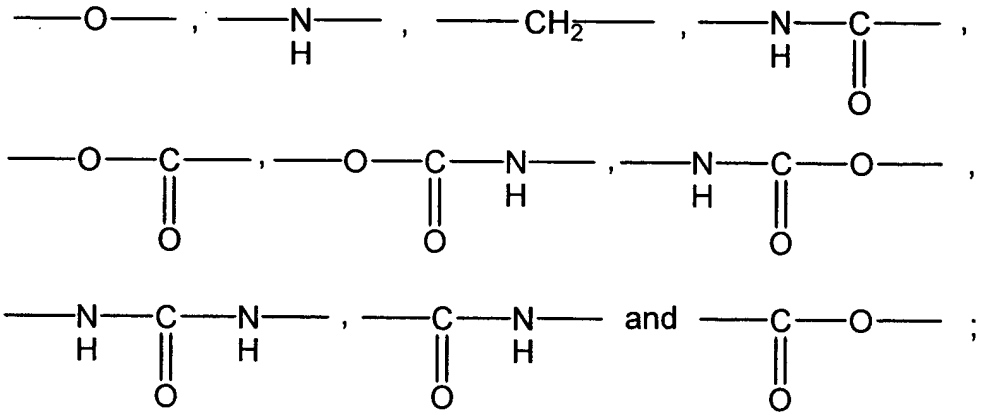
each R_A, R_B, R_E and R_D are individually H, or any two of R_A, R_B, R_E and R_D together form a bond, or R_A, R_B, R_E and R_D together with the atoms to which they are bonded form a six-membered aromatic ring;

each R_A', R_B', R_E' and R_D' are individually H, or any two of R_A', R_B', R_E' and R_D' together form a bond, or R_A', R_B', R_E' and R_D' together with the atoms to which they are bonded form a six-membered aromatic ring;

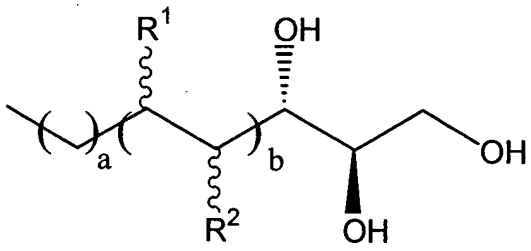
each x, y and z are individually either 0 or 1;

w is 1 to 5;

-Q- is selected from the group consisting of



-T is a moiety of formula (2)



(2);

R^1 and R^2 are each individually selected from the group consisting of H and OH;

a is 0 to 3;

b is 0 to 3;

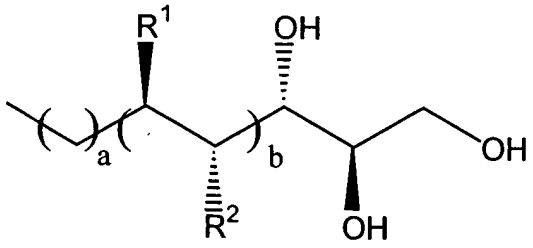
~~~~ indicates that the chirality of the carbon atom to which it is attached is either R or S; and

Surf designates where the moiety attaches to said surface.

20. The substrate of claim 19, further comprising:
(iii) a monolayer comprising said moieties,
wherein said monolayer does not fail a cell patterning test at 12 days.

21. The substrate of claim 19, further comprising:
(iv) a base,
wherein said surface layer is on said base.

22. The substrate of claim 21, wherein -T is a moiety of formula (2')



(2').

23. The substrate of claim 22, wherein a is 1, b is 1 and at least one of R^1 and R^2 is OH.

24. The substrate of claim 22, wherein -L- contains 8 to 18 carbon atoms.
~~~~

25. The substrate of claim 24, wherein -L- contains 1 or 0 double bonds, or 1 triple bond.

26. The substrate of claim 22, wherein -L- is an alkylene containing 6 to 18 carbon atoms.

27. The substrate of claim 22, wherein -Q- is -O- or $-CH_2-$.

28. The substrate of claim 23, wherein -L- is an alkylene containing 6 to 18 carbon atoms, and -Q- is -O-.

29. A substrate, comprising:

(i) a surface layer comprising gold, and

(ii) a monolayer comprising moieties, on at least a portion of said surface layer,

wherein said moieties are alkanethiolate moieties; and

said monolayer does not fail a cell patterning test at 12 days.

30. A cell chip, comprising:

(A) the substrate of claim 19, and

(B) cells, on said substrate.

31. A cell chip, comprising:

(A) the substrate of claim 20, and

(B) cells, on said substrate.

32. A cell chip, comprising:

(A) the substrate of claim 22, and

(B) cells, on said substrate.

33. A cell chip, comprising:

(A) the substrate of claim 24, and

(B) cells, on said substrate.

34. A cell chip, comprising:

(A) the substrate of claim 26, and

(B) cells, on said substrate.

35. A cell chip, comprising:

(A) the substrate of claim 28, and

(B) cells, on said substrate.

36. A cell chip, comprising:

(A) the substrate of claim 29, and

(B) cells, on said substrate.

41. A method of making a substrate, comprising contacting a surface with an alkanethiol of formula 1 or the enantiomers of formula (1);

HS——L——Q——T (1),

wherein -L- is $-(A_x-B_y-E_z-D)_w-$;

each A, B, E and D are individually $C(R_AR_A')$-, $-C(R_BR_B')$-, $-C(R_ER_E')$-,and $-C(R_DR_D')$-, respectively;

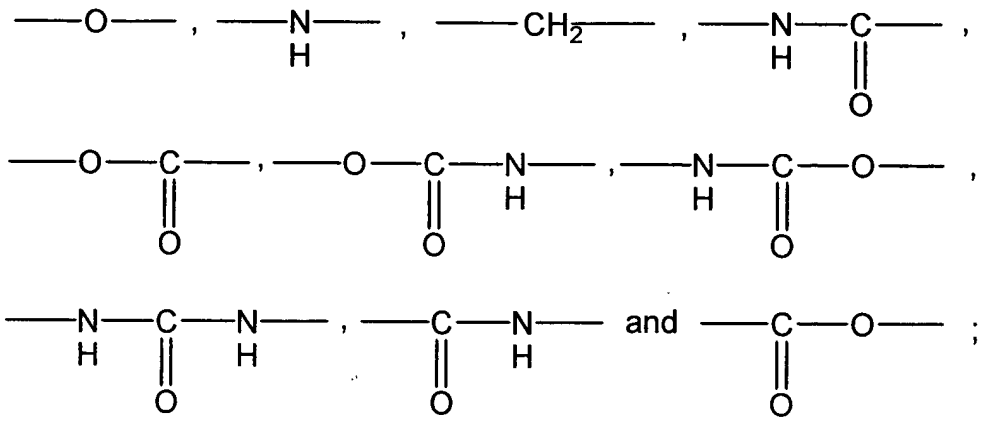
each R_A, R_B, R_E and R_D are individually H, or any two of R_A, R_B, R_E and R_D together form a bond, or R_A, R_B, R_E and R_D together with the atoms to which they are bonded form a six-membered aromatic ring;

each R_A', R_B', R_E' and R_D' are individually H, or any two of R_A', R_B', R_E' and R_D' together form a bond, or R_A', R_B', R_E' and R_D' together with the atoms to which they are bonded form a six-membered aromatic ring;

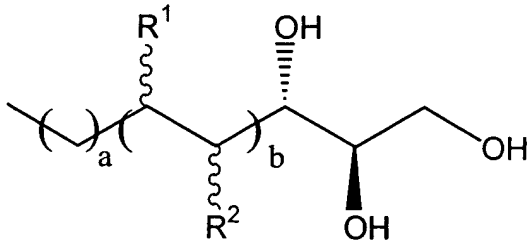
each x, y and z are individually either 0 or 1;

w is 1 to 5;

-Q- is selected from the group consisting of



-T is a moiety of formula (2)



(2);

R^1 and R^2 are each individually selected from the group consisting of H and OH;

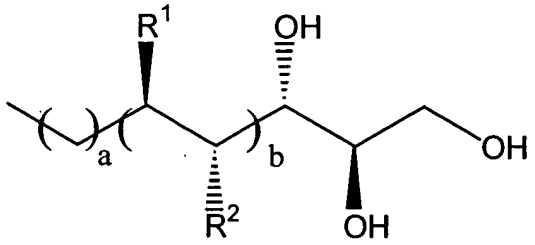
a is 0 to 3;

b is 0 to 3; and

~~~ indicates that the chirality of the carbon atom to which it is attached is either R or S;

wherein said surface comprises gold.

43. The method of claim 41, wherein -T is a moiety of formula (2')



(2').

44. The method of claim 43 wherein a is 1, b is 1, at least one of R^1 and R^2 is OH, -L- is an alkylene containing 6 to 18 carbon atoms, and -Q- is -O-.
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49. A method of making a cell chip, comprising:
contacting cells with the substrate of claim 19.

50. The method of claim 49, further comprising allowing said cells to proliferate.

51. A method of making a cell chip, comprising:
contacting cells with the substrate of claim 20.

52. The method of claim 51, further comprising allowing said cells to proliferate.

53. A method of making a cell chip, comprising:
contacting cells with the substrate of claim 22.

54. The method of claim 53, further comprising allowing said cells to proliferate.

55. A method of making a cell chip, comprising:
contacting cells with the substrate of claim 28.

56. The method of claim 55, further comprising allowing said cells to proliferate.

57. A method of making a cell chip, comprising:
contacting cells with the substrate of claim 29.

58. The method of claim 57, further comprising allowing said cells to proliferate.